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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/661,398	09/12/2003	H. Robert Horvitz	01997/548003	7921

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EXAMINER	
HIBBERT, CATHERINE S	

ART UNIT	PAPER NUMBER
1636	

NOTIFICATION DATE	DELIVERY MODE
07/24/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/661,398	HORVITZ ET AL.	
	Examiner	Art Unit	
	CATHERINE HIBBERT	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 22-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 22-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4 August 2008 has been entered.

Applicants' Amendment to the Claims filed 4 August 2008 has been received and entered. Applicants' submittal of Rule 132 Affidavit, filed 4 August 2008, is acknowledged. Claims 4-21 are cancelled. Claims 1-3 and 22-34 are pending and under examination.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows: The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph

of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosures of the prior-filed applications, Application Nos. 60/437,821 and 60/410,160 fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. While the disclosure of the instant application provides support for the genes *lin(n4256)* and *lin-65,* the Provisional Applications 60/437,821 and 60/410,160 do not provide any support for the *lin(n4256)* and *lin-65* genes as there is no mention of either of these genes in the Provisional Applications.

Therefore, claims 23-30 do not receive the Priority dates of the provisional applications.

Applicants state that the disclosures of the prior-filed application, Provisional Application No. 60/410,160 does provide support for the *lin-15A* and *lin-38* genes, pointing to page 16, third paragraph, for description of the *lin-15A* and *lin-38* genes.

Therefore, claims 22 and 32 do receive the Priority dates of the Provisional Application No. 60/410,160.

Response to Arguments

Any objections/rejections not repeated herein are withdrawn herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make

and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 and 22-34 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record as stated in the office action mailed 7 February 2008 and for reasons below, because the specification, while being enabling for: a method for identifying a candidate compound that may have potential as a compound that treats a neoplasia, comprising: (a) contacting a *C. elegans* vulval precursor cell comprising a "loss of function" mutation in a Class B synMuv gene and a second "loss of function" mutation in a "Class A synthetic multivulval gene", with a candidate compound, and (b) detecting cell proliferation in the contacted cells compared to control cells, does not reasonably provide enablement for *any cell type* or for *any* cell in a nematode or for *any* isolated mammalian cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicant's arguments and have been fully considered but are respectfully found not persuasive for reasons of record and herein.

Applicants response is to traverse the rejection. Applicants submit that given (1) the Examples in the specification and (2) the high degree of structural and functional homology between members of the synthetic multivulval signaling pathway and the members of the Ras-signaling and Rb-signaling pathways; a skilled artisan in the field of molecular biology could use the method of amended claims 1, 23, 27, and 31 in a variety of cells (e.g., additional nematode cell types and mammalian cell types).
As the Office has noted above, the specification teaches the use of precursor vulval

tissue in the method of amended claims 1, 23, 27, and 31. In addition to the teachings of the specification, Applicants submit that, at the time of filing of the present application, Ras family genes and Rb family genes were known to be structurally and functionally conserved between C. elegans and mammals, and expressed in a variety of cell types. On this point, Applicants direct the Office's attention to the disclosed Declaration by Dr. H. Robert Horvitz. Dr. Horvitz states (paragraph 2):

Prior to the filing date of the application, Ras family genes and Rb family genes were known to be structurally and functionally conserved between C. elegans and mammals, and expressed in a variety of cell types. Based on the known conservation of Ras family and Rb family genes in numerous cell types, and the Examples in the specification of the present application, I would have expected, at the time of filing, one skilled in the art of molecular biology to have been capable of using the methods claimed in the present application that utilize a cell having a loss of function mutation in mep-1, lin(n3628), lin(n4256), or lin-65, and a second loss of function in a Class A synMuv gene, to identify candidate compounds for treating neoplasia using any one of a variety of cell types including various C. elegans and mammalian cells.

Moreover, the specification teaches that Class A synMuv and Class B synMuv genes are structurally and functionally homologous to members of the Ras- and Rb- signaling pathways, respectively. Accordingly, based on the known conservation of Ras family and Rb family genes, and the Examples in the specification of the present application, Applicants submit that one skilled in the art of molecular biology could use, without undue experimentation, the methods claimed in the present application that utilize a cell

having a loss of function mutation in mep-1, lin(n3628), lin(n4256), or lin-65, and a second loss of function in a Class A synMuv gene, in a variety of cell types (for example, other C. elegans or mammalian cells).

Applicants argue that "With regard to the knowledge in the art concerning the conservation of Ras family and Rb family genes", Applicants "direct the Office's attention to Santos and Nebreda (FASEB J. 3:2151-2163, 1989; submitted with the Reply to Office Action filed October 30, 2007; "Santos") and Saito et al. (Cancer Invest. 20:264-275, 2002; Exhibit B)". In particular, Applicants submit that Santos states:

> Ras genes appear to be ubiquitous in eukaryotic cells, and yeasts are the lowest organisms found to possess functional ras genes. The remarkable degree of conservation between species as far apart in evolution as yeast and human strongly suggests that ras gene products play a fundamental role in key cellular processes. (Pg. 2152, left column, second paragraph).

and Saito et al. states:

> Many other [C. elegans] genes have been found to regulate the ras signal-transduction pathway .... [I]t is important to mention that several of these genes are presently novel but will likely have mammalian counterparts. (Pg. 270; emphasis added). Regarding the conservation of members of the Rb gene family, the specification states (page 1, lines 19-28): Retinoblastoma (Rb) family proteins are mammalian tumor suppressors that regulate cell proliferation. This pathway is conserved among a variety of species, including the nematode, Caenorhabditis elegans. (Emphasis added). Clearly, the Ras-signaling and Rb-signaling families are highly conserved. As such, Applicants submit that one skilled in the art would be able to use the methods of the amended claims in a variety of cell types without undue experimentation. This basis for rejection should be withdrawn. As a further basis of rejection, the Office states that "the prior art teaches that use of isolated mammalian cells are not predictable models of cancer" (Office Action, pg. 9) and that "more work will be necessary to ... provide a precise picture of how these processes relate to one another" (Office Action, pg. 8).

Applicant argues that "the amended claims are directed to an *in vitro* method of identifying *candidate* compounds useful for the treatment of a neoplasia. These are *candidate* compounds. The amended claims are not directed to an *animal model of cancer*. Applicants submit that, at the time of filing, *in vitro* screening assays of candidate compounds using cells were standard in the art. Applicants further submit that, at the time of filing, cell culture models of cancer were known to share many aspects of cancer (e.g., unregulated cell proliferation)".

Furthermore, Applicants argue that "the presently claimed methods are used to identify *candidate* compounds. Clearly, such candidate compounds will require further testing in animal models of cancer to verify their therapeutic potential *in vivo*. There can be no question that the specification enables screening methods to identify candidate compounds".

Applicants further submit "that 35 U.S.C. § 112, first paragraph, does not require that the specification disclose the mechanism of action of a particular compound identified using the claimed methods. Enablement simply requires that the specification, in combination with the knowledge in the art, teaches the skilled artisan how to make and use the claimed invention". For the above reasons, Applicants submit "that the specification meets the enablement requirement for claims 1-3 and 22-34".

Applicant's arguments and Rule 132 Affidavit, filed 4 August 2008, have been fully considered but are respectfully found not persuasive because the amended claims are directed to a method for identifying a candidate compound for treating a neoplasia,

said method comprising: (a) contacting a cell comprising a first "loss of function" mutation in a Class B synMuv gene (mep-1, lin(n3628), lin(n4256), and lin-65) and a second "loss of function" mutation in a Class A synthetic multivulval gene, with a candidate compound; and (b) detecting cell proliferation in the contacted cells compared to control cells. Further limitations are drawn to cells in a nematode (claims 2, 25, 29 and 33) or in an isolated mammalian cell (claims 3, 26, 30 and 34), or to where the Class A synthetic multivulval gene is lin-15A or lin-38 (claims 22, 24, 28 and 32).

Although Applicant's arguments are well taken that Applicant's invention "could be performed in a number of cells, including different nematode cell types and mammalians cell types", Applicant's claims are drawn to *any* and *all* types of cells.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)). The following factors are relevant in the instant case:

Nature of the invention: The nature of Applicant's invention involves determination of potential anti-neoplastic activity by a process involving contacting a

mutant cell with a candidate compound and detecting cell proliferation levels in the contacted cells compared to control cells. While the nature of this experiment is technologically feasible within a certain limited scope, the results of performing this assay would not necessarily identify a compound having anti-neoplastic activity and the scope of the claims extends well beyond the scope enabled by the application.

Breadth of the claims: Claims are broadly drawn to any type of cell (claims 1, 22-24, 27-28 and 31-32), any type of cell in a nematode (claims 2, 25, 29 and 33) or any type of an isolated mammalian cell (claims 3, 26, 30 and 34). However, the model for the synMuv Class A and Class B mutants is performed using precursor vulval tissue in the nematode *C. elegans* (see especially specification). Even the breadth of the more limiting claims which read on *any* cell in a nematode or *any type* of an isolated mammalian cell, would still be too broad to ensure the same outcome which is obtained using synMuv mutants in the precursor vulval tissue of *C. elegans*.

State of the Prior Art and Predictability: The state of the prior art teaches that the SynMuv phenotype is revealed when mutations are present in genes from both classes A and B. Several class B genes have been identified as components of the Rb transcriptional regulatory-complex and "this finding raises the possibility of cross talk between cell-cycle/transcriptional controllers and known regulators of vulval development including members of the RTK/Ras/map kinase pathway. (Fay and Han), "The Synthetic Multivulval Genes of C. elegans: Functional Redundancy, Ras-Antagonism, and Cell Fate Determination", in Genesis: 26:279-284 (2000). Fay and Han further point out that "multiple mechanisms could be operating in the generation of

the SynMuv phenotype. This possibility seems even more likely given that two distinct classes of mutants are required for the expression of the phenotype. The basic observation that class A and B genes are genetically redundant does not mean that both classes carry out identical biological functions. Malfunctions in two distinct pathways could converge to produce the observed defect. For example, the combination of cell-cycle and transcriptional defects could interfere with cell fusion, if both timing and gene expression are critical to this process. Clearly more work will be necessary to sort out these possibilities and provide a more precise picture of how these processes relate to one another." (p. 283, ¶ 4).

Furthermore, the state of the prior art teaches that the use of isolated mammalian cells are not predictable models of cancer. For example, Zips *et al.* ["In Vitro and In Vivo Evaluation of new Anticancer Agents" In Vivo. 2005 Jan-Feb;19(1):1-7] recites:

> "It is obvious that cells in culture represent an artificial and simplified system. Unlike the situation *in vitro*, a tumor is a 3-dimensional complex consisting of interacting malignant and non-malignant cells. Vascularisation, perfusion and, thereby drug access to the tumor cells are not evenly distributed and this fact 'consists' an important source of heterogeneity in tumor response to drugs that does not exist *in vitro*. Therefore, prediction of drug effects in cancer patients based solely on *in vitro* data is not reliable and further evaluation in animal tumor systems is essential." (p.3 col.2)

Direction provided by the inventor and Existence of working examples: For the instant invention, the applicant does not provide direction or evidence of working examples to establish whether the invention is enabled for *all cell types*, all cells in a nematode, or all types of isolated mammalian cells. Therefore, the skilled artisan seeking to practice the invention according to its full scope would not be able to predict which embodiments within the broad scope of the claims could be used as claimed.

Unpredictability and Undue Experimentation: Because of the reasons stated above, the unpredictability of the outcome of the neoplasia assay would require undue experimentation with various cell types to determine whether the assay would be able to identify candidate compounds for treating neoplasia.

Therefore, claims 1-3 and 22-34 stand rejected under 35 U.S.C. 112, first paragraph, as lacking an enabling disclosure, for reasons of record and for reasons above.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3 and 22-34 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants arguments have been fully considered but are not persuasive.

Applicants response filed 4 August 2008 traverses the rejection and states that Claims 1, 23, 27, and 31 have been amended to specify that the requirement for a nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 24, 26, 28, or 2, respectively, *includes* the loss of function mutation *in addition* to the requirement for a 95% sequence identity to the SEQ ID NOS. Applicants submit that "the sequence of SEQ ID NOS: 24, 26, 28, and 2 are the wildtype sequences and, therefore, the limitation of 95% sequence identity to SEQ ID NO: 24, 26, 28, or 2 includes the loss of function mutation.

Applicants arguments have been fully considered but are not persuasive because the currently amended Claims 1, 23, 27 and 31 are still unclear because it is unclear whether the requirement for "a nucleic acid sequence having at least 95% sequence identity to the respective sequences of SEQ ID NO:s 24, 26, 28 and 2, is for a sequence which *includes* the "loss of function" mutation, or alternatively, whether the claims are directed to a "loss of function" mutation *in addition* to the requirement for a 95% sequence identity to the SEQ ID NO:s, which would then represent a sequence which is less than 95% sequence identity to the respective sequences of SEQ ID NO:s 24, 26, 28 and 2. For example, the claims, as written, encompass embodiments that do not require the loss of function mutation to be in the respective sequences of SEQ ID NO:s 24, 26, 28 and 2. Therefore, the metes and bounds of Applicants' invention can not be determined.

Claims 2-3, 22, 24-26, 28-30 and 32-34 are indefinite insofar as they depend from claims 1, 23, 27 and 31.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CATHERINE HIBBERT, whose telephone number is (571)270-3053. The examiner can normally be reached on M-F 8AM-5PM, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/NANCY VOGEL/
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